Contains Nonbinding Recommendations

Draft Guidance on Mesalamine

Active ingredient: Mesalamine

Form/Route: Delayed Release Capsules /Oral

Recommended studies: 3 studies

1. Type of study: Fasting
   Design: Single-dose, partially or fully replicated crossover design, in vivo
   Strength: 400 mg
   Subjects: Normal healthy males and females, general population. Females should not be pregnant, and if applicable, should practice abstention or contraception during the study.
   Additional comments: Other study designs are acceptable if appropriate. Specific recommendations are provided below.

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2. Type of study: Fed
   Design: Single-dose, partially or fully replicated crossover design, in vivo
   Strength: 400 mg
   Subjects: Normal healthy males and females, general population. Females should not be pregnant, and if applicable, should practice abstention or contraception during the study.
   Additional comments: Other study designs are acceptable if appropriate. Specific recommendations are provided below.

Analytes to measure (in appropriate biological fluid): Mesalamine in plasma

Bioequivalence based on (90% CI): Mesalamine

Additional comments regarding the BE study with PK endpoints:

(1) Applicants may consider using a reference-scaled average bioequivalence approach for mesalamine. If using this approach, the applicant should provide evidence of high variability in the bioequivalence parameters (i.e., within-subject variability > 30%) for the reference product. For general information on this approach refer to the Progesterone Capsule Guidance for additional information regarding highly variable drugs.

(2) For both fasting and fed studies, the following PK parameters are recommended to be evaluated: Log-transformed AUC_{8-48}, AUC_{0-t}, and C_{max}, where AUC_{8-48} is the area under the plasma concentration vs. time curve from 8 to 48 hours, AUC_{0-t} is the area under the curve from 0 hours to the last measurable time point, and C_{max} is the maximum plasma concentration. Applicants should have extensive sampling points around T_{max} to have accurate estimation of C_{max} and T_{max}, and at least four non-zero measurements of concentration are recommended before T_{max} and between T_{max} and 24 hours. Other partial AUCs may be evaluated as supporting material to evaluate similarity of drug release throughout the gastrointestinal tract.

(3) As AUC_{0-t} is recommended in place of $AUC_{0-\infty}$, the last sampling time point should be at least at 72 hours.

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3. Type of study: In vitro comparative dissolution study

Strength:	400 mg
Apparatus:	USP Apparatus 2 (paddle)
Stage 1:	2 hours in 0.1 N HCl at 100 rpm (500 mL)
Stage 2:	Each of (1) pH 4.5 Acetate buffer at 50 rpm (2) pH 6.0 Phosphate buffer at 50 rpm (3) pH 6.5 Phosphate buffer at 50 rpm (4) pH 6.8 Phosphate buffer at 50 rpm (5) pH 7.2 Phosphate buffer at 50 rpm (6) pH 7.5 Phosphate buffer at 50 rpm
Volume:	900 mL
Temperature:	37ºC
Sample times:	The sampling time should be at least 150 minutes or as needed for profile comparison when applicable

Waiver request of in vivo testing: Not applicable

Dissolution test method and sampling times:

Please note that a **Dissolution Methods Database** is available to the public at the OGD website at http://www.accessdata.fda.gov/scripts/cder/dissolution/. Please find the dissolution information for this product at this website. Please conduct comparative dissolution testing on 12 dosage units each of all strengths of the test and reference products. Specifications will be determined upon review of the application.

Due to a concern of dose dumping of drug from this drug product when taken with alcohol, the Agency currently requests that additional dissolution testing be conducted using various concentrations of ethanol in the dissolution medium, as follows:

Testing Conditions: 900 mL, 0.1 N HCl, USP apparatus 2 (paddle) @100 rpm, with or without alcohol;

Test 1: 12 units tested according to the proposed method (with 0.1N HCl), with data collected every 15 minutes for a total of 2 hours

Test 2: 12 units tested by substituting 5% (v/v) of test medium with Alcohol USP and data collection every 15 minutes for a total of 2 hours

Test 3: 12 units tested by substituting 20% (v/v) of test medium with Alcohol USP and data collection every 15 minutes for a total of 2 hours

Test 4: 12 units tested by substituting 40% (v/v) of test medium with Alcohol USP and data collection every 15 minutes for a total of 2 hours

Both test and RLD products must be tested accordingly and data must be provided on individual unit, means, range and %CV.